

The University of Chicago

COMPARATIVE STUDIES ON  
CALCIUM GLUCONATE  
AND  
OTHER CALCIUM SALTS

A DISSERTATION SUBMITTED TO THE  
GRADUATE FACULTY IN CANDIDACY FOR  
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

By

ARNOLD LEO LIEBERMAN, M.D.

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## COMPARATIVE STUDIES ON CALCIUM GLUCONATE AND OTHER CALCIUM SALTS\*

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About two years ago, Professor Luckhardt asked me to observe the comparative pharmacologic effects following the intravenous injection of calcium lactate and calcium gluconate in unanesthetized dogs. The methods were, briefly, an exposure of the carotid vessels under ether anesthesia, recovery of the dogs from the immediate effects of the operation, and an injection of the salts in question while the animals were awake. Blood pressure tracings, pulse, and respiratory readings were made then over a period of from thirty minutes to one and a half hours. The full details of this series appeared elsewhere,<sup>1</sup> so that it is necessary here only to summarize the results. Charts 1 and 2 show concisely the elevation of the blood pressure with the simultaneous pulse retardation. Also, the relatively evanescent effects of the lactate salt as compared to the gluconate stands out strikingly. Digitalis effects were quite noticeable. Recognizable heart block, arrhythmias, coupling of beats, and other digitalis-poisoning effects were induced repeatedly. Here, again, the gluconate salt was somewhat slower in producing these results as compared with the lactate compound, but, once produced, they tended to persist a much longer time. They would appear as soon as five minutes after the intravenous administration of the calcium salt and would persist sometimes an hour or more. Billigheimer<sup>2</sup> had previously noted the digitalis effects of calcium

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\* Work done on grant from the Sandoz Fund.

\* From the Hull Physiological Laboratories of the University of Chicago.

\* Read before the Section on Pharmacology and Therapeutics at the Eighty-Second Annual Session of the American Medical Association, Philadelphia, June 10, 1931.

1. Lieberman, A. L.: *J. Pharmacol. & Exper. Therap.* **50**: 65 (Sept.) 1930.

2. Billigheimer, E.: *Klin. Wchnschr.* **8**: 724 (April 16) 1929.

which, to me, appear to be well worth further study. Also, emphasis was placed on the danger of intravenous calcium therapy; sudden clotting was noted several times as a result of the well known but frequently forgotten tendency of calcium to increase the coagulability of the blood.

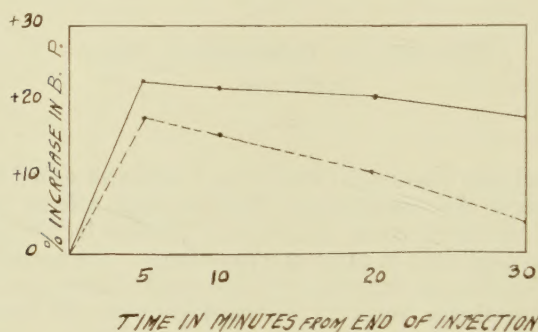


Chart 1.—Average of series of eight determinations: solid line, gluconate; broken line, lactate.

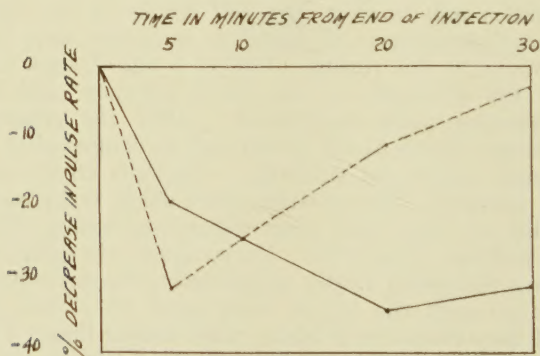


Chart 2.—Average of series of eight determinations: solid line, gluconate; broken line, lactate.

Before proceeding to the study of further cardiac effects of calcium, it was thought advisable to make some detailed observations on the best methods of administering calcium salts. Some of the results already obtained appear to be of immediate practical interest. The changes in the calcium levels of the blood and urine are especially commented on here.

Calcium gluconate can be given subcutaneously in repeated and adequate amounts (parathyroidectomized dogs being kept alive in this fashion<sup>3</sup>) without causing the irritation and necrosis that other calcium salts do when so injected. Szenteh<sup>4</sup> was able to report decreased postpartum hemorrhage by using this compound. That this procedure will promptly elevate the blood calcium was conclusively shown in normal and parathyroidectomized dogs.<sup>5</sup>

There has been some confusion in the literature as to the proper time of giving calcium compounds when administered orally. Thus, Roe and Kahn<sup>6</sup> showed definitely that large amounts of calcium lactate, when

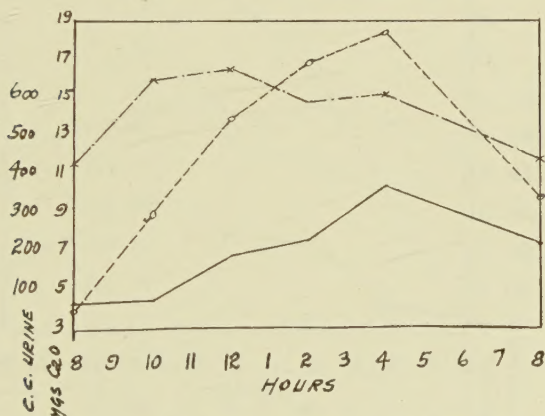


Chart 3.—Average in ten cases; no breakfast; 10 Gm. of calcium gluconate by mouth: solid line, urine volume; broken line with circles, urine calcium; line of dots and dashes with crosses, blood calcium.

given intimately mixed with food, failed to cause a rise in blood calcium. On these grounds they advocate giving the calcium on an empty stomach. In some studies on urine I<sup>7</sup> came to the conclusion that the amount of intestinal absorption depended to a decisive extent on the length of time the calcium compounds were permitted to stay in the bowel. When given on

3. Lieberman, A. L., and Szurek, S. A.: *J. Pharmacol. & Exper. Therap.* **51**: 333 (March) 1931.

4. Szenteh, S.: *Zentralbl. f. Gynäk.* **53**: 1828 (July 20) 1929.

5. Lieberman, A. L.: *J. Pharmacol. & Exper. Therap.*, to be published.

6. Roe, J. H., and Kahn, B. S.: Absorption of Calcium from the Intestinal Tract of Human Subjects, *J. A. M. A.* **88**: 980 (March 26) 1927.

7. Lieberman, A. L.: *J. Pharmacol. & Exper. Therap.* **50**: 71 (Sept.) 1930.

an empty stomach there appeared to be a marked tendency for the production of diarrhea with its attendant phenomena. As food tended to minimize this hydragogue salt action of the calcium compounds, it seemed that giving it after a meal would cause greater absorption and less distress.

To settle the point, about thirty individuals were taken and submitted to procedures described in detail elsewhere.<sup>8</sup> The blood and urine calcium changes were

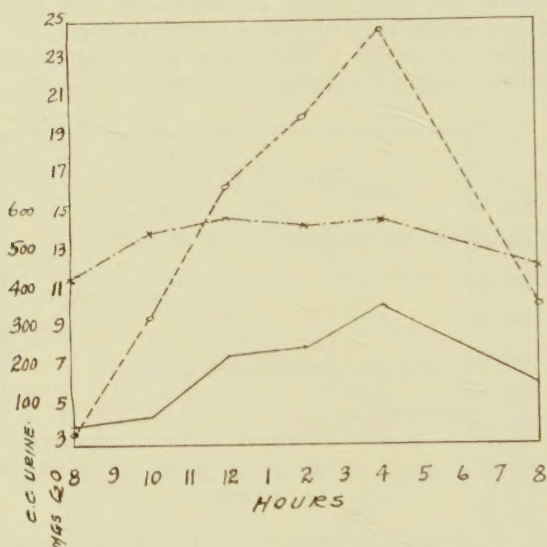


Chart 4.—Average of ten cases; 10 Gm. of calcium gluconate by mouth after standard breakfast: lines as in chart 3.

traced preceding and following the administration of calcium gluconate as follows: Ten received 10 Gm. orally on an empty stomach; ten received 10 Gm. after a standard breakfast; five had 20 cc. of the 10 per cent solution<sup>9</sup> injected deep in the buttocks while receiving no food; five others had a similar injection following a standard breakfast. Charts 3, 4, 5 and 6 show in summary form the results obtained. Charts 3 and 4 seem to show that calcium gluconate is absorbed a trifle better and gives more persistent elevation of the blood and urinary calcium when given after a meal. Sub-

8. Lieberman, A. L.: Studies in Calcium, J. Pharmacol. & Exper. Therap., to be published.

9. Calcium gluconate-Sandoz, N. N. R., 1931.



jectively there was an immense difference: the patients had no complaints to speak of when the compound was given after breakfast, while there was a very definite diarrheal tendency when they received the calcium on an empty stomach. With severe diarrhea there appears to be no blood calcium elevation of any moment, the medication being rushed through and out of the bowel before being given a chance to absorb.<sup>5</sup>

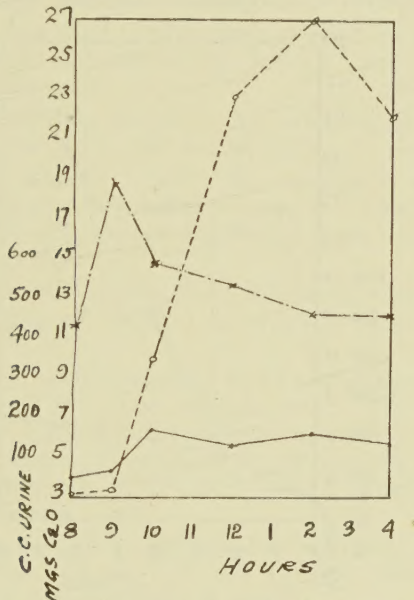


Chart 5.—Average of five cases without breakfast; 20 cc. of calcium gluconate deep in muscles; lines as in chart 3.

As can be seen, the blood calcium reached its maximum about the fourth hour after oral administration. Intramuscular injection gives the peak within the first hour. This is of practical importance when speed of action is desired. It seems hardly worth while to take a chance on sudden death and give the calcium intravenously when an intramuscular injection will attain the same end in so short a time and without any risk.

On further inspection of the urine calcium curves, it will be noted that there is a lag in the rise of the calcium here as compared with the blood level. However, even if there is no quantitative relationship

between blood and urine calcium, there appears to be a distinct qualitative correlation. As long as the hourly output of urine in the individual is above, say, 10 mg. of calcium an hour, there is little danger of that individual developing hypocalcemia with its attendant symptoms. Conversely, the continued output of, say, 30 to 40 mg. an hour would be quite clear evidence of a state of hypercalcemia which will lead to its typical signs and symptoms if continued. Because of this factor

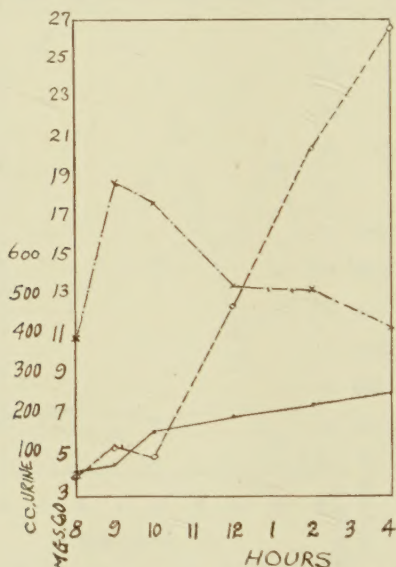


Chart 6.—Average of five cases with standard breakfast; 20 cc. of calcium gluconate deep in muscles; lines as in chart 3.

of lag, however, a low urine calcium followed by a rise some four to six hours after a dose of calcium would be an indication of a fall in blood calcium and of the advisability of repeating the dose. In cases in which parathyroid extract is being given, post thyroidectomy or in infants with tetany, this should be of practical importance. It is certainly much easier to take a specimen of urine than to take a sample of blood.

As regards dosage of calcium gluconate when being given by mouth: After perusing the charts it seems fair to say that 10 Gm. of the powder when split into, say, three doses and given about half an hour after

meals should be sufficient to maintain an adequate calcium level without at the same time tending to produce a hypercalcemia.

#### SUMMARY AND CONCLUSIONS

1. Calcium gluconate was taken as a most convenient representative calcium salt and studied as to dosage and effects on human beings and dogs when given orally, subcutaneously and intravenously.

2. This compound can be given in repeated and adequate amounts subcutaneously without causing either irritation or necrosis.

3. Three or four grams a day after meals appears to be about the right dose for an adult.

4. Blood calcium attains its maximum elevation within an hour after subcutaneous or intramuscular administration of calcium and within four hours after being given orally.

5. Intravenous calcium therapy is dangerous because of the menace of sudden intravascular clotting and death.

6. Urinary calcium appears to be a qualitative index of the state of the blood calcium level. Whether this is true in all pathologic conditions remains to be seen. A urinary value of about 10 to 20 mg. an hour appears to be most desirable in avoiding either a hypercalcemia or a hypocalcemia.

7. Highly suggestive digitalis-like effects of calcium were observed and the need for further investigation of this phase of the problem is noted.







